Sub C4 B3

18. (twice amended) In a method for treating cancer or other proliferative disorder comprising administering an effective amount of at least one mitotic phase cell cycle inhibitor or topoisomerase inhibitor to an animal in need of such treatment, the improvement comprising administering to said animal prior to administration of said mitotic phase cell cycle inhibitor or topoisomerase inhibitor an effective amount at least one cytoprotective α,β unsaturated aryl sulfone compound, wherein the mitotic phase cell cycle inhibitor and topoisomerase inhibitor are other than an α,β unsaturated aryl sulfone compound, and wherein the animal is protected from the cytotoxic side effects of the administration of said mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

Remarks

Applicants' representative thanks Examiner Bahar for the telephonic interview conducted on June 18, 2002.

The specification has been amended to correct a typographic error. No new matter has been added by this amendment. A "marked-up" version of the replacement paragraph, as required under 37 C.F.R. 1.121(b)(1)(iii), is included herein as Appendix A.

Claims 1-22 are pending in the application. Claims 8-11 have been cancelled without prejudice to the filing of a divisional application. Claims 1 and 18 have been amended. Support for the amended claims is found in the specification at pg. 13, lns. 22-29; pg. 14, lns. 13-15; pg. 15, lns. 1-3; and Examples 3, 4, 5, 6, and 7-12. A "marked up" version of the amended claims has been included herein as Appendix B, as required by 37 C.F.R. 1.121(c)(1)(ii).

Response to section 103(a) rejection

Claims 1-7 and 12-22 are rejected under 35 U.S.C. 103(a) as allegedly rendered obvious by Reddy et al. WO 99/18608 (Reddy) and Griggs, Embase Abstract AN 1998287056 (Griggs). Applicants respectfully disagree.

The present claims are directed to methods in which an animal (inclusive of humans) is protected from cytotoxic side effects of mitotic phase cell cycle or topoisomerase inhibitors by administering at least one cytoprotective α,β unsaturated aryl sulfone compound before treatment with the mitotic phase cell cycle or topoisomerase inhibitor.

During the June 18, 2002 telephonic interview, the Examiner indicated that the claims as written allegedly encompassed methods in which the subsequently administered mitotic phase cell cycle or topoisomerase inhibitor was also an α,β unsaturated aryl sulfone compound. Applicants disagree with this interpretation of the claims. However, in the interest of advancing prosecution, claims 1 and 18 have been amended to recite that the claimed mitotic phase cell cycle or topoisomerase inhibitor is "other than an α,β unsaturated aryl sulfone compound."

The α,β unsaturated aryl sulfones are known to exhibit cytotoxicity towards tumor cells; however, the precise mechanism by which this cytotoxicity occurs is not known. It is therefore not clear whether the α,β unsaturated aryl sulfones are mitotic phase cell cycle or topoisomerase inhibitors. In any case, the present specification discloses that the claimed mitotic phase cell cycle and topoisomerase inhibitors can be compounds other than α,β unsaturated aryl sulfones (see, *e.g.*, pg. 13, lns. 22-29 and pg. 14, lns. 13-15). Examples 3, 4, 5, 6, and 7-12 of the present specification also show the practice of the claimed methods using mitotic phase cell cycle or topoisomerase inhibitors that are other than an α,β unsaturated aryl sulfone. Thus, the amendments to claims 1 and 18 are supported by the specification.

The Examiner alleges that Reddy teaches the cytoprotective qualities of α,β unsaturated aryl sulfone compounds, because these compounds are cytotoxic to tumor cells but "spare" normal cells. With this interpretation of Reddy in hand, the Examiner then alleges that it is obvious to substitute α,β unsaturated aryl sulfone compounds for amifostine, the cytoprotective compound disclosed in Griggs, thus arriving at the presently claimed invention. Applicants respectfully disagree with the Examiner's interpretation of these references.

why not?

To establish a *prima facie* case of obviousness, a reference or combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicant's disclosure. In re Dow Chemical Company, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Here, there is nothing in Reddy or Griggs that would motivate one of ordinary skill in the art to combine the teachings of these references to produce the presently claimed invention, or provide a reasonable expectation of success in doing so.

Reddy discloses the use of α,β unsaturated aryl sulfone compounds for the treatment of cancer, and notes that these compounds are not cytotoxic to normal cells. Reddy does not disclose the administration of a second and separate cytotoxic compound, or suggest that the α,β unsaturated aryl sulfone compounds can be used to protect normal cells from a subsequently administered mitotic phase cell cycle or topoisomerase inhibitor.

According to the Examiner, the *absence* of α,β unsaturated aryl sulfone toxicity in normal cells reported in Reddy is equivalent to the actively cytoprotective effects of α,β unsaturated aryl sulfones as presently claimed. However, one of ordinary skill in the art would not consider the absence of a particular drug effect in a cell to indicate a positive interaction between the drug and a cell.

For example, the absence of alpha or beta-2 receptor effects from drugs designed to bind to the beta-1 receptor[1] is attributed to the lack of interaction between that drug and beta-2 or alpha receptors, and not to some active shielding or protective attribute of the drug with respect to these receptors. Likewise, one of ordinary skill in the art would not conclude from reading Reddy that the α,β unsaturated aryl sulfone compounds were actively protecting the normal cells.

Griggs discloses that amifostine protects normal cells from the cytotoxic effects of alkylating agents, paclitaxel, and radiation. Amifostine is an organic thiophosphate homolog of cytsteamine; see entry for "amifostine" from The Merck Index (12th Edit.), Budavari et al., eds., Merck & Co., Inc., Whitehouse Station, NJ, 1996, attached. It was also known at the time the present application was filed that more amifostine is taken up by normal cells than by tumor cells, which accounts for the drug's cytoprotective properties. See, *e.g.*, the abstract titled "Cytoprotectant Amifostine Approved" accessed from

http://www.slip.net/~mcdavis/database/amifos2.htm

on July 18, 2002 (attached), which references Spencer CM et al., (1995), *Drugs* 50: 1001-1031.

There is no mention in Griggs of α,β unsaturated aryl sulfone compounds, let alone their use as a cytoprotectant equivalent to amifostine. As can be seen from the Merck Index entry, *supra*, the chemical structures of the α,β unsaturated aryl sulfones and amifostine are completely unrelated. There is also no evidence in Reddy or Griggs that the α,β unsaturated aryl sulfones

[1] *I.e.*, beta-1 antagonists such as Brevibloc (esmolol), used to treat cardiac fibrillation or supraventricular tachycardia.

have a differential uptake in normal vs. tumor cells akin to amifostine. Moreover, the mechanism of action of amifostine and the α,β unsaturated aryl sulfones appears to be different; amifostine protects normal cells from alkylating agents (see Griggs), while the α,β unsaturated aryl sulfones do not (see the present specification at pg. 51, lns. 16-19 and Table 6).

Thus, one of ordinary skill in the art would not be motivated to combine the teachings of Reddy and Griggs to arrive at the present invention because 1) Reddy does not disclose or suggest the cytoprotective properties of the α,β unsaturated aryl sulfone compounds; 2) Reddy does not disclose or suggest the administration of α,β unsaturated aryl sulfone compounds prior to administering a separate mitotic phase cell cycle or topoisomerase inhibitor; 3) the chemical structure of the α,β unsaturated aryl sulfones and amifostine are unrelated; and 4) there is no evidence in Reddy that the α,β unsaturated aryl sulfones and amifostine share similar pharmacokinetic characteristics.

Even assuming *arguendo* that Reddy somehow teaches the use of α,β unsaturated aryl sulfones as cytoprotectants, "the mere fact that the components at issue are functional or mechanical equivalents" is not sufficient, absent some other indication in the prior art, that amifostine and α,β unsaturated aryl sulfones are interchangeable. M.P.E.P. 2144.06. The Examiner has not identified any teaching in the prior art showing that amifostine and the α,β unsaturated aryl sulfones are equivalent cytoprotectants[2]. In fact, their disparate chemical structures, different mechanisms of action, and potentially dissimilar pharmacology show that amifostine and the α,β unsaturated aryl sulfones are not equivalent. Thus, ~~even if the~~ Examiner's interpretation of Reddy were taken as correct, one of ordinary skill in the art would not be motivated to combine the teachings of the two references to arrive at the presently claimed invention. The different chemical structures and mechanisms of amifostine vs. the α,β unsaturated aryl sulfones as cytoprotectants would also not provide one of ordinary skill in the art with a reasonable expectation of success that the present invention could be produced by combining the teachings of the Griggs and Reddy.

On pg. 4 of the Detailed Action, the Examiner states that Griggs was cited only for the prospect that cytoprotective agents are known to be used with mitotic cell cycle inhibitors. As

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[2] Indeed, the Examiner has shown nothing in the prior art to indicate that the α,β unsaturated aryl sulfones have cytoprotectant properties.

discussed above, there is no indication in the prior art that the α,β unsaturated aryl sulfones can be used to protect normal cells against mitotic phase cell cycle inhibitors. Regardless, the generalized disclosure in Griggs that cytoprotectants in general are used with paclitaxel cannot, even in combination with Reddy, provide the motivation to make the presently claimed invention. There must be a specific suggestion contained within either Griggs or Reddy to use the α,β unsaturated aryl sulfones as cytoprotectants for these reference to be properly combined. As discussed above, this suggestion does not exist.

The Examiner also argues that the combination of the α,β unsaturated aryl sulfones from Reddy with the paclitaxel from Griggs would be obvious because both compounds are known to treat cancer, and "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition for the same purpose" (see Detailed Action, pg. 3). However, the present claims are not directed to a composition comprising an α,β unsaturated aryl sulfone and paclitaxel. Rather, the present claims recite methods in which cytoprotection is conferred to an animal by administration of α,β unsaturated aryl sulfones prior to treatment of the animal with a mitotic phase cell cycle or topoisomerase inhibitor. The Examiners argument is therefore not pertinent to the present claims. In any case, there is no teaching or suggestion in the prior art to use α,β unsaturated aryl sulfones to protect an animal from the cytotoxic effects of mitotic phase cell cycle or topoisomerase inhibitors.

Because there is no teaching or suggestion for using α,β unsaturated aryl sulfone compounds as cytoprotectants prior to Applicants' disclosure, the Examiner's interpretation of Reddy and Griggs must derive from hindsight reconstruction using the present specification. As the Federal Circuit held in In re Gorman, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991), it is improper to combine prior art teachings to render the claimed invention obvious, absent some "teaching, suggestion or incentive supporting the combination." *See also* Uniroyal Inc. v. Rudkin-Wiley Corp. 5 USPQ2d 1434 (Fed. Cir. 1988) ("When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself") and In re Rouffet, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998) ("When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references). Thus, the prior art documents as a whole must provide the motivation for making the

combination, and this motivation must be found apart from Applicant's disclosure. In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Absent such motivation, however, the Examiner may not use the claimed invention as a template to piece together elements from various unrelated prior art documents, or use an isolated teaching from a reference to fill gaps in the prior art, to arrive at an obviousness rejection. In re Gorman, *supra*, at 1888; In re Fritch, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

Here, the cited references carry no relationship except that imposed by the present specification and claims. Once removed from the context of Applicant's disclosure, the references fragment into a collection of unrelated disclosures with little bearing on the claimed invention.

In sum, the cited references do not, either alone or in combination, suggest to one of ordinary skill in the art that the claimed invention can be made or practiced with a reasonable expectation of success. Any motivation to combine the teachings of the cited references is the result of impermissible hindsight. Thus, the Examiner has not established a *prima facie* case of obviousness and the 35 U.S.C. 103(a) rejection of claims 1-7 and 12-22 is improper and should be withdrawn.

Response to the Examiner's Suggestion that the Cytoprotectant Qualities of the α,β unsaturated aryl sulfones are Inherent in Reddy and Griggs

On pg. 4 of the Detailed Action, the Examiner states that "the administration of the alpha, beta unsaturated styryl [sic] sulfone compound, would inherently encompass all the qualities of the compound (i.e., cytoprotection) since a compound and its properties cannot be mutually exclusive." Applicants disagree that the cited art inherently discloses the protection of animals from the cytotoxic effects of mitotic phase cell cycle or topoisomerase inhibitors by administering α,β unsaturated aryl sulfones prior to treatment of the animal with the mitotic phase cell cycle or topoisomerase inhibitors.

a compound & its properties cannot be mutually exclusive

A characteristic of a claimed invention is inherent in the prior art only if it necessarily flows from the teachings of the prior art. In re Oelrich and Divigard, 212 USPQ 323 (CCPA 1981). Furthermore, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte

Levy, 17 USPQ2d 1461, 1464 (Bd.Pat.App. & Int.1990) (emphasis added). The Examiner cannot make such a showing here.

As discussed above, neither Reddy nor Griggs teach that α,β unsaturated aryl sulfones have cytoprotective qualities. The only cytoprotectant disclosed in Griggs, amifostine, is completely unrelated structurally to the α,β unsaturated aryl sulfones and appears to differ in its mechanism of action and pharmacokinetics. Also, Reddy does not disclose the subsequent administration of a mitotic phase cell cycle or topoisomerase inhibitor which is other than an α,β unsaturated aryl sulfone. Reddy also does not suggest that a secondary cytotoxin can or should be administered after administration of the α,β unsaturated aryl sulfones. Methods which comprise protecting animals from the cytotoxic effects of mitotic phase or cell cycle inhibitors through the prior administration of α,β unsaturated aryl sulfones do not necessarily flow from the teachings of Reddy and Griggs. These references therefore cannot inherently disclose the presently claimed invention.

Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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Appendix A – "Marked-up" Version of Amended Replacement Paragraph as Required Under 37 C.F.R. 1.121(b)(1)(iii)

Paragraph on pg. 54, lns. 2-12:

The cytoprotective activity of the same [lstyryl] <u>styryl</u> benzylsulfones was determined as follows. Normal human HFL-1 cells were plated at a cell density of 1.0 x 10^5 cells per well in six culture plates. Styryl benzylsulfone was added 24 hours later at a final concentration of either 2.0 or 10 μM. The time of styryl sulfone addition was designated as time zero. Paclitaxel (250 nM) was added at either time zero, or 24 hours after time zero. The total number of viable cells was determined, as described above, after 96 hours of paclitaxel treatment. A compound was deemed to be active if the number of viable cells following the combination treatment was higher than the number of cells after treatment with paclitaxel alone. The data are set forth in Table 7.

Appendix B – "Marked-up" Version of Amended Claims as Required Under 37 C.F.R. 1.121(c)(1)(ii)

1. (once amended) A method for protecting an animal from cytotoxic side effects of the administration of a mitotic phase cell cycle inhibitor or a topoisomerase inhibitor comprising administering to the animal, in advance of administration of said inhibitor, an effective amount of at least one cytoprotective α,β unsaturated aryl sulfone compound, wherein the mitotic phase cell cycle inhibitor and topoisomerase inhibitor are other than an α,β unsaturated aryl sulfone compound.

18. (twice amended) In a method for treating cancer or other proliferative disorder comprising administering an effective amount of at least one mitotic phase cell cycle inhibitor or topoisomerase inhibitor to an animal in need of such treatment, the improvement comprising administering to said animal prior to administration of said mitotic phase cell cycle inhibitor or topoisomerase inhibitor an effective amount at least one cytoprotective α,β unsaturated aryl sulfone compound, wherein the mitotic phase cell cycle inhibitor and topoisomerase inhibitor are other than an α,β unsaturated aryl sulfone compound, and wherein the animal is protected from the cytotoxic side effects of the administration of said mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

Cytoprotectant Amifostine Approved

The FDA has approved a new cytoprotective agent -- amifostine (Ethyol/US Bioscience) -- for reducing the cumulative renal toxicity associated with repeated cisplatin therapy in patients with advanced ovarian cancer. Amifostine is an organic thiophosphate prodrug that is rapidly dephosphorylated in tissues to a pharmacologically-active free thiol. This thiol compound binds and detoxifies reactive cisplatin metabolites, and also scavenges free radicals generated in tissues exposed to cisplatin. Since amifostine reaches a higher concentration in normal tissue relative to tumor tissue, it is able reduce cisplatin's renal toxicity without compromising the antitumor efficacy. First developed to protect tissues against radiation damage, amifostine has since proved to be effective for protecting against hematologic toxicity in patients receiving cisplatin, cyclophosphamide, and/or mitomycin, and to reduce cisplatin- induced nephrotoxicity, ototoxicity, and neurotoxicity. In clinical trials, patients treated with amifostine showed a reduction in neutropenia-related fever and sepsis and spent fewer days in the hospital and/or on antibacterial therapy, compared with patients who did not receive amifostine. Moreover, fewer patients discontinued therapy before completing the scheduled number of treatment cycles. Amifostine is given intravenously as a 15-minute infusion of 910 mg/m2 starting 30 minutes prior to cisplatin therapy.

The drug is rapidly cleared from plasma; distribution half-life is less than one minute and elimination half-life is about 8 minutes. Less than 10% of amifostine remains in the plasma 6 minutes after administration. The most common side effects are transient reduction in blood pressure, nausea, vomiting, somnolence, and sneezing. Less common side effects include flushing, hypocalcemia. and hiccups. Antiemetics reduce the nausea (pretreatment with dexamethasone or metoclopramide has no effect on pharmacokinetics). Contraindications include hypotension, dehydration, hypocalcemia, or sensitivity to aminothiol compounds or mannitol (the vehicle). US Bioscience is continuing Phase II and III trials to evaluate the effects of ethyol for protecting against radiation damage in patients treated for tumors of the rectum, cervix, lung and neck. It is also under investigation for its ability to sensitize a tumor to therapy. It is in trial for use with Bristol-Myer's taxol, allowing escalation of the dose to more than twice the dosage currently used in clinical practice. US Bioscience developed amifostine and owns the patents; Alza has exclusive marketing rights in the US for five years; Schering-Plough is marketing the drug in Europe; and Lilly is planning to introduce it in Canada. (Spencer CM, Goa KL. Drugs 1995;50:1001-1031. Additional information from Alza.)

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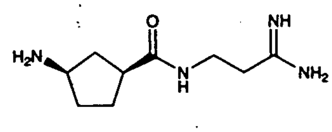
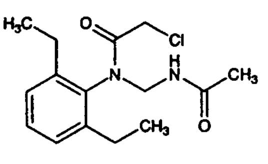
Antibiotic substance produced by *Streptomyces flavochromogenes* isolated from Japanese soil (Shiuoka Prefecture). Isoln and structure: S. Nakamura *et al., J. Antibiot.* **14A,** 103 (1961); S. Nakamura, *Chem. Pharm. Bull.* **9,** 641 (1961). Identity with myxoviromycin: S. Nakamura *et al., J. Antibiot.* **14A,** 163 (1961). Prepn: Katsube, Saito, **Japan.** pat. **21,418('68)** (to Sumitomo), *C.A.* **70,** 87135q (1969). Synthesis of amidinomycin and *trans* isomer: H. Paul *et al., Arch. Pharm.* **301,** 512 (1968). Crystal and molecular structure: M. Kaneda *et al., J. Antibiot.* **33,** 778 (1980).



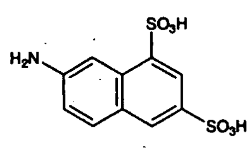
Sulfate, $C_9H_{18}N_4O.H_2SO_4$, plates or needles from water + methanol, dec 285-288°. $[\alpha]_D^{21}$ −3.9° (c = 3). Absorption spectra: S. Nakamura, *loc. cit.* Soluble in water. Practically insol in ether, benzene, ethyl acetate, methanol, ethanol, butanol, acetone.
THERAP CAT: Antiviral.

420. Amidochlor. *N-[(Acetylamino)methyl]-2-chloro-N-(2,6-diethylphenyl)acetamide; N*-acetamidomethyl-2-chloro-2′,6′-diethylacetanilide; MON-4621; Limit. $C_{15}H_{21}ClN_2O_2$; mol wt 296.80. C 60.70%, H 7.13%, Cl 11.95%, N 9.44%, O 10.78%. Plant growth regulator for cool season grasses. Prepn: **Neth.** pat. **Appl. 7,207,261;** K. W. Ratts, **U.S.** pat. **3,830,841** (1972, 1974 both to Monsanto); K. W. Ratts, J. P. Chupp, *J. Org. Chem.* **39,** 3745 (1974). Use as plant growth regulator: K. W. Ratts *et al.,* **U.S.** pat. **3,829,306** (1974 to Monsanto). Effect on growth and seedhead suppression of annual bluegrass: A. M. Petrovic *et al., Agron. J.* **77,** 670 (1985); of wild and cultivated proso millet: J. L. Carpenter, H. J. Hopen, *HortScience* **20,** 942 (1985); on established turfgrass: P. C. Bhowmik, *Proc. 5th Int. Turfgrass Res. Conf.* 735 (1985).



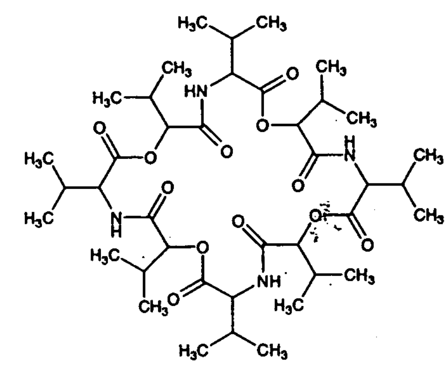
Crystals from methanol, mp 148-149°.
USE: Turf growth regulator.

421. Amido-G-Acid. *7-Amino-1,3-naphthalenedisulfonic acid;* 2-naphthylamine-6,8-disulfonic acid; amino-G-acid. $C_{10}H_9NO_6S_2$; mol wt 303.32. C 39.60%, H 2.99%, N 4.62%, O 31.65%, S 21.14%. Prepd by sulfonation of β-naphthylamine: Fierz-David, Braunschweig, *Helv. Chim. Acta* **6,** 1146 (1923).



Tetrahydrate, fine monoclinic needles. Sol in water, less sol in alc. Soly in water at 20°: 9.24 g in 100 g of satd soln.
USE: Manufacture of dyes.

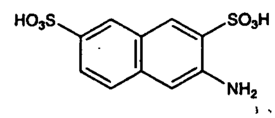
422. Amidomycin. $C_{40}H_{68}N_4O_{12}$; mol wt 797.00. C 60.28%, H 8.60%, N 7.03%, O 24.09%. Antibiotic substance produced by an unidentified *Streptomyces* culture (PRL 1642). Composed of 4 moles each of D-(−)-valine and D-(−)-α-hydroxyisovaleric acid, linked alternately by ester and amide bonds to form a 24-membered ring: Vining, Taber, *Can. J. Chem.* **35,** 1109 (1957). Structure studies: Shemyakin *et al., Tetrahedron Letters* **1963,** 351, *Tetrahedron* **19,** 995 (1963).



D-amino acids only

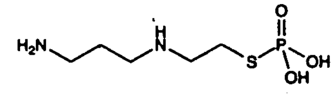
Needles from dilute ethanol or petr ether, mp 192°. $[\alpha]_D^{26}$ +19.2° (c = 1.2 in ethanol). Neutral reaction. Practically insol in water. Readily sol in most organic solvents. Primarily active against yeasts.

423. Amido-R-Acid. *3-Amino-2,7-naphthalenedisulfonic acid;* 2-naphthylamine-3,6-disulfonic acid. $C_{10}H_9NO_6S_2$; mol wt 303.32. C 39.60%, H 2.99%, N 4.62%, O 31.65%, S 21.14%. Prepd by treating 2-hydroxy-3,6-naphthalenedisulfonic acid with ammonium sulfite and ammonium hydroxide: Petitcolas, Josué, *Bull. Soc. Chim. France* **1952,** 89.



Crystals or powder. Soluble in water. Solutions show a violet-blue fluorescence.
USE: Manufacture of dyes.

424. Amifostine. *2-[(3-Aminopropyl)amino]ethanethiol dihydrogen phosphate ester; phosphorothioic acid S-[2-[(3-aminopropyl)amino]ethyl] ester;* aminopropylaminoethyl thiophosphate; ethiofos; gammaphos; SAPEP; NSC-296961; WR-2721; YM-08310; Ethyol. $C_5H_{15}N_2O_3PS$; mol wt 214.23. C 28.03%, H 7.06%, N 13.08%, O 22.41%, P 14.46%, S 14.97%. Thiophosphate derivative of cysteamine, *q.v.*; provides normal cells with selective protection against the toxic effects of cancer chemotherapy and radiation treatment. Prepn of monohydrate: J. R. Piper *et al., J. Med. Chem.* **12,** 236 (1969); J. R. Piper, T. P. Johnston, **U.S.** pat. **3,892,824** (1975 to Southern Res. Inst.). Differential radioprotective activity: J. M. Yuhas, J. B. Storer, *J. Nat. Cancer Inst.* **42,** 331 (1969). Mechanism of action study: G. D. Smoluk *et al., Cancer Res* **48,** 3641 (1988). Bioavailability: L. Fleckenstein *et al., Pharmacol. Ther.* **39,** 203 (1988). Clinical pharmacokinetics: L. M. Shaw *et al., ibid.* 195. HPLC determn in plasma: N. F. Swynnerton *et al., Int. J. Radiat. Oncol. Biol. Phys.* **12,** 1495 (1986). Review of development as radioprotector: D. Q. Brown *et al., Pharmacol. Ther.* **39,** 157-168 (1988); of role in chemotherapy: R. L. Capizzi *et al., Cancer* **72,** 3495-3501 (1993); M. Treskes, W. J. M. van der Vijgh, *Cancer Chemother. Pharmacol.* **33,** 93-106 (1993).



Monohydrate, white solid from methanol/ether, mp 160-161° (dec). LD_{50} in mice (mg/kg): 700 i.p. (Piper, Johnston).